Remarks

In the Office Action mailed July 13, 2004, claims 44, 54-74, and 77-80 were withdrawn from consideration by the Examiner. Accordingly, claims 39-43, 45-53, 75, and 76 are presently under consideration. The Examiner has rejected claims 39-43, 45-53, 75, and 76 under 35 U.S.C. § 103(a) over Bhat *et al.*, in view of Tedder *et al.*, Anderson *et al.*, and Goldenberg. The specific grounds for objection, and Applicants' response thereto, are set out in detail below.

Rejection under § 103(a)

The Examiner has rejected claims 39-43, 45-53, 75, and 76 based on the primary reference of Bhat *et al.*, asserting:

> "Bhat et al teach methods of depleting B cells by administering to a host antibodies which bind B cell markers (column 2 lines 6-13), such as CD19, CD20 and CDD22 (column 2 lines 24-27). Bhat et al contemplate using these methods to treat autoimmune diseases, such as multiple sclerosis (column 1 lines 33-36)."

While the Examiner admits that "Bhat *et al.*do not teach the use of a combination of anti-CD20 antibody, anti-CD22 epitope B antibody, and IFN-β," he contends that this acknowledged deficiency of Bhat *et al.* is remedied by the secondary references of Tedder *et al.* Anderson *et al.* and Goldenberg. Applicants respectfully traverse.

The Federal Circuit has set forth a two-part test for obviousness. Thus, when combining references to make out a *prima facie* case of obviousness, the Examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001).

The rejection here fails to satisfy either part of the test. First, contrary to the Examiner's assertion, Bhat does not "teach methods of depleting B cells by administering to a host antibodies

which bind B cell markers * * * *, such as CD19, CD20 and CD22" nor does Bhat "contemplate using these methods to treat autoimmune diseases, such as multiple sclerosis." Bhat alleges that antibodies against the antigen CDIM can be used to kill B-cells (see column 2, lines 8-13) and states that B-cells express CD19, CD20 and CD22 (see column 2, lines 24-27). Bhat also asserts that an antibody against CDIM might be used to treat autoimmune disease (see column 3, liens 25-27), although no data in support of this proposition are provided[1]. Nowhere, however, does Bhat teach or suggest using antibodies against CD19, CD20, or CD22 to treat autoimmune disease; this, despite explicit recognition by Bhat that B-cells express CD19, CD20, and CD22. This deficiency is not remedied by any of the secondary references.

Moreover, with respect to the involvement of B cells in autoimmune disease, Bhat *et al.* states:

> "[t]hese autoimmune diseases can be extremely destructive, as is evidenced by diabetes, rheumatoid arthritis, neuronal diseases, such as multiple sclerosis, and the like. While in many cases, the disease is associated with T-cell attack, in some of the diseases, there may be a B-cell component, and in other diseases, such as rheumatoid arthritis and lupus nephritis, the primary mediator may be B-cells."

See, column 1, lines 32-39 (emphasis added). Thus, Bhat states that *many* cases of autoimmune disease are associated with T-cell attack but that *some* diseases may have a B-cell component. Notably, contrary to the Examiner's assertion, Bhat does not describe multiple sclerosis as one of the diseases that *may* be mediated by B-cells.

Bhat's statements therefore exemplify nothing more than uncertainty surrounding the role of B cells in autoimmune disease. Bhat states that B-cells may be defined by expression of surface markers such as CD19, CD20, and CD22 but, contrary to the Examiner' assertion, fails to teach or suggest that antibodies against these markers might be used to treat autoimmune disease. The only suggestion that antibodies against CD19, CD20, and/or CD22 can be used to treat autoimmune disease is based on applicants' own specification. The use of applicants' specification in this manner is specifically the type of hindsight reconstruction of the claimed invention that is proscribed by the Federal Circuit:

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[1] Moreover, as described below, the skilled artisan would have had no reasonable expectation that antibodies against CDIM could be used to treat autoimmune disease.

> As this court stated, "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements"). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint to defeat the patentability of the claimed invention. Such an approach would be an "illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).

In sum, Bhat would not have provided one of ordinary skill in the art with the motivation to treat autoimmune disease by inactivating or depleting B-cells as recited in the current claims. This lack of motivation is further evidenced by the failure of those skilled in the art to follow the alleged teachings of Bhat, despite the clear need in the art for methods of treating autoimmune disease. Indeed, antibodies to B cell surface antigens were reported in the scientific literature as early as 1987, (*see*, for example, Mason *et al.* (1987), *Value of monoclonal anti-CD22 (p135) antibodies for the detection of normal and neoplastic B lymphoid cells,* Blood, Vol. 69(3):836-40 -- attached hereto as Exhibit A). If it would have been obvious to use anti-B-cell antibodies to treat autoimmune disease based upon the teachings of Bhat it is curious that the field failed to recognize this allegedly obvious fact until the present invention, despite the clear clinical need for such treatments.

Nothing in Tedder *et al.* , Anderson *et al.* and Goldenberg, alone or in combination, addresses the uncertainty with regard to the role of B-cells in autoimmune disease or cures the deficiencies of Bhat *et al.* The Examiner's discussion amounts to nothing more than an improper hindsight reconstruction of applicant's claimed invention, and the rejection should be withdrawn.

Third, the person of ordinary skill in the art would not have had a reasonable expectation of success in using B-cell antibodies to treat autoimmune disease and the second prong of the tests for a *prima facie* case of obviousness also is not met. Specifically, nothing in Bhat *et al.*'s would have led the person of ordinary skill in the art to believe that inactivating or depleting B-

cells would be an effective treatment for autoimmune disease, because the antibody described by Bhat is not B cell specific.

Bhat characterizes the CDIM epitope, which binds the monoclonal antibody 216, thus:

> "[t]he epitope is structurally related to, but distinct from, the "I" and "i" antigens present on adult and chord red blood cells (RBS's) respectively, . . ." (column 2, lines 38-40).

This statement is incorrect. In fact, Bhat's own data show that mAb 216 reacts with (1) the i antigen present on cord RBC, (2) a ligand on human B lymphocytes, and (3) certain autoantigens. *See* Bhat *et al.* (1993), *Human antilipid A monoclonal antibodies bind to human B cells and the i antigen on cord red blood cells*, J. Immunol., Vol. 151(9): 5011-5021 (attached hereto as Exhibit A). More accurately, therefore, Bhat *et al* teach a monoclonal antibody reactive with a carbohydrate ligand present on various cells, including some B cell populations.

The failure of Bhat *et al.* to teach a B cell specific antibody raises further concern about the therapeutic usefulness and success of Bhat *et al.*'s alleged teaching. Because Bhat *et al.*'s antibody is not B-cell specific the Examiner is misguided in concluding that one skilled in the art would have sought to employ B-cell specific antibodies to treat autoimmune disease.

More importantly, the 1993 publication of Bhat *et al.* -- showing that the CDIM antigen is present on chord red blood cells -- would have taught away from using Bhat *et al.*'s antibody as an *in vivo* therapy. One of skill in the art would have certainly appreciated the harm in delivering a non-specific antibody as an *in vivo* therapy. Nothing in Tedder *et al.*, Anderson *et al.* and Goldenberg, alone or in combination can cure the inaccuracies of Bhat *et al.*

In conclusion, the Examiner has failed to set forth any proper motivation to combine the cited references and relies upon an improper hindsight reconstruction of applicants' invention in setting forth the instant rejection. Moreover, even if a motivation to make the combination could be found, there would have been no reasonable likelihood of success in the combination. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness and the applicants respectfully submit that rejection should be withdrawn.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional fees are required for the filing of this paper, Applicants authorize the Commissioner to charge any deficiency to Deposit Account No. 08-1641.

Respectfully submitted,

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